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| EXAMINER |
|---|
| FOLEY, SHANON A |

| ART UNIT | PAPER NUMBER |
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| 1648 | 15 |

DATE MAILED: 08/12/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/719,340 | Applicant(s) KAPPES ET AL. | |
|---|---|---|---|
| | Examiner Shanon Foley | Art Unit 1648 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *10 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *37-86* is/are pending in the application.

4a) Of the above claim(s) *50-64 and 66-86* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-49 and 65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6,10,13,14*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

### *Election/Restrictions*

Applicant's election with traverse of group I in Paper No. 12 is acknowledged. The traversal is on the ground(s) that groups II and III share the special technical feature of group I according to PCT Rule 13.2 and should be examined together.

Although Applicant is correct that groups II and III both require the instant cell line to practice the methods of both groups, it is maintained that groups II and III lack unity of invention with group I. A special technical feature that links the unity of invention in claims is only allowed for specific categories of combinations, such as a first product and the first method of using that product, see 37 CFR § 1.475 (b). Group I includes an immortalized cell as the first product and the first method of using the immortalized cell to detect HIV. Any subsequent method of using the cell product lacks unity of invention and is properly restricted.

The requirement is still deemed proper and is therefore made FINAL.

Claims 50-64 and 66-86 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected group, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 12. Claims 37-49 and 65 are under consideration.

### *Claim Objections*

Claims 39 and 48 are objected to because of the following informalities: "infers" is presumably "confers". Appropriate correction is required.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 38, 41 and 43-49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 38 recites that the "cell originates from HeLa". It is unclear how a cell "originates" from another. Is the cell also a HeLa cell, or a derivative of a HeLa cell, or divided from a cell line of HeLa cells? If the instant cell is a derivative of a HeLa cell, how is the cell derived from a HeLa cell?

Claim 41 is vague and indefinite for reciting "to a degree similar to" in reference to sensitivity to HIV. What are the metes and bounds of the degrees and what is intended by "similar"?

Claim 43 is indefinite because there is no correlative step in the method that unites the conclusion of the method with the preamble of the claim. Also, the purpose of the method is unclear. The method is drawn to detecting the presence of HIV by adding a sample known to have at least one HIV to a cell expressing a reporter gene that is activated in the presence of HIV. Why would detection by the marker gene in the cell be required when it is known that the sample contains HIV? Claim 45 is drawn to further isolating the virus after detecting its presence. However, if the sample is known to contain HIV, the virus is already isolated in the sample. Therefore, it is unclear what applicant intends from the method. This rejection affects claims 44-49.

Claims 46 and 49 are drawn to a "primary" HIV virus. Is "primary" referring to HIV-1? Page 7, lines 1-3 define "primary HIV" as virus isolated from different sources. However, it remains unclear what a "primary" virus is. What would a secondary virus be?

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 43-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detecting virus particles, does not reasonably provide enablement for detecting one HIV virus or determining accurate *in vivo* viral titers with the instant cell line. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to a method of detecting HIV by contacting a cell line expressing specific receptors with a composition known to comprise at least one HIV and quantifying viral titers. One skilled in the art would not be able to detect one HIV virus in a sample due to the detection limits of the various reporter systems and replication capacities of different HIV strains and subtypes. Splenlehauer et al. (Virology. 2001; 280: 292-300) teaches the degree of luciferase activity and HIV titers of different viruses, see Figure 2 on page 294. The figures demonstrate that a viral titer of at least 0.03 to 0.12 $TCID_{50}$ is required to produce reporter activity, depending on viral subtype. The instant invention is drawn to using a HeLa-based cell line, a human cervical cancer cell line. The skilled artisan would doubt that the instant cell line would be accurate for determining viral titers, as in instant claim 44. Roos et al. (Virology. 2000; 273: 307-315) teaches that MAGI cell lines, macaque mammary tumor cells that use HIV

LTR to express the β-gal reporter gene (see Chackerian et al. (Journal of Virology. 1997; 71 (5): 3932-3939), first paragraph under "materials and methods), are not representative of HIV host cell infections, see the second paragraph of the first column on page 312. Therefore, due to the reduced propagation of tumor-based cell lines, accurate viral quantitation would not be indicative of a host's viral titer. Roos et al. also teaches that the antiviral drug AZT has limiting quantitative influences on β-gal expression, see figure 5 on page 311. Therefore, if a sample is derived from a patient taking AZT is contacted with the instant cell line, reporter gene sensitivity will diminish. The instant working examples indicate that the cells are infected with "infectious units" of HIV. However, there is no definition for how many viral particles an "infectious unit" represents. There is no working example or teaching in the disclosure drawn to detecting a sample containing a single HIV or correlating *in vivo* viral titer with the *in vitro* method.

Therefore, due to the titers of HIV required to activate reporter genes, the lack of definition provided in the specification for "infectious units", the degree of sensitivity of reporter genes in relationship to the particular viral strain analyzed and antiviral drugs, the reduced replication capacity of HIV in HeLa-derived cell lines, the lack of correlative data with respect to *in vivo* viral titer and *in vitro* quantitative detection, it is determined that undue experimentation would be required of the skilled artisan to use the invention in its full scope.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 37-49 and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Littman et al. (US 6,258,527) and Chackerian et al. (Journal of Virology. 1997; 71 (5): 3932-3939).

Claims 37-42 are drawn to an immortalized, HeLa-derived cell expressing CCR5, CXCR4, and CD4 receptors and a reporter gene under control of an HIV LTR promoter that is activated upon HIV infection. Claim 65 is drawn to the cell line in a kit. Claims 43-49 are drawn to a method of detecting HIV in a sample by contacting the cell line with a composition comprising HIV and assaying for expression of the reporter gene. HIV is a primary HIV-1 virus that is further isolated and quantified.

Littman et al. teaches a transformed human cell that expresses CD4 and CC-CKR5, i.e., CCR5, and a reporter gene, or CD4 and CXC-CR4, i.e., CXCR4 and a reporter gene. The reporter gene is luciferase or a green fluorescent protein under regulation of an HIV LTR, see claims 1-3 and 5-7 and column 6, lines 10-15. Activation of the reporter gene occurs upon HIV infection, see column 6, lines 16-29. The cell is an immortalized HeLa cell line, see column 25, lines 55-61. Littman et al. also teaches the cell line in a kit, see column 5, lines 33-43. Although Littman et al. does not explicitly teach quantifying virus particles by the amount of reporter gene expression, the reference does teach labeling the various receptors to quantify the β-chemokine used in HIV infection, see column 5, lines 5-20. This calculation would be analogous to the number of viral particles within the infected cell.

Chackerian et al. teaches sMAGI cells expressing CD4 and CD5, or CD4 and CXCR4 receptors with a green fluorescent reporter protein, see the first paragraph under materials and methods and the "Construction..." section on page 3933 and the results section.

Neither reference teaches expressing CD4 and CCR5 and CXCR4 receptors in the same cell.

However, one of ordinary skill in the art at the time the invention was made would have been motivated to express all three receptors, CD4 and CCR5 and CXCR4, in the same cell line to enable infection of any strain, type, or clade of HIV virus. Chackerian et al. teaches that cell lines expressing CD4 and CXCR4 are only susceptible to T-tropic HIV isolates, while cell lines expressing only CD4 and CD5 receptors were susceptible to M-tropic HIV, see the discussion section. One of ordinary skill in the art at the time the invention was made would have been motivated to incorporate the CD4 and the HIV co-receptors to inhibit replication and infectivity blocks inherent in cells deficient in the a required receptor, see the discussion section of Chackerian et al. as well as the abstract and column 1, lines 52-67 of Littman et al. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for producing the claimed invention because it is taught by Littman et al. and Chackerian et al. which co-receptors are required for various types of HIV infection and how to co-express the different receptors in cells for successful viral infection. Therefore, the invention as a whole would have bee prima facie obvious to one of ordinary skill in the art, absent unexpected results to the contrary.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon Foley whose telephone number is (703) 308-3983. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (703) 308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4426 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Shanon Foley
August 7, 2002

JAMES HOUSEL 8/9/02
SUPERVISORY PATENT EXAMINER
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